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ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/711,724	TABIN ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,17-27,29-36,42-49,63-76,78-91* is/are pending in the application.

4a) Of the above claim(s) *4,5,18,19,24,25,31,79,80 and 85-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,7,17,20-23,26,27,29,30,32-36,42-49,63-76,78 and 81-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *4,5,18,19,24,25,31,79,80 and 85-91* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/20/2001*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Election/Restrictions

Applicant's election with traverse of methods of detection based on gene expression, claims 3, 6-7, 17, 19-23, 26-27, 29-30, 32-36, 42-49 and 63-76 in Paper No. 10/03/2002 is acknowledged. The traversal is on the ground(s) that the claims encompass overlapping subject matter and the search is not burdensome. Applicant's argument has been fully considered but is not deemed persuasive because applicant has neither submitted evidence nor admitted on the record that the species are obvious variants, as required at page 3 of the office action mailed 2/27/2002. As such, it remains that the species are patentably distinct inventions, distinct for reasons set out in the paper mailed 2/27/02, and the required searches, while overlapping, are not coextensive and would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

Claim 19 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Applicant submitted new claims 78-91 by amendment in Paper No. 3/12/02, subsequent to restriction election in Paper No. 10/03/2002. Newly submitted claims 78 and 81-84 are generic or drawn to the elected species, detection by expression of particular genes (including use of reported genes). Newly submitted claims 79-80 and 85-86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 3-7, 17-27, 29-36, 42-49, 63-76, 78 and 81-84, drawn to the genus of method of detection, classified in class 435, subclass 7.1 or 7.2.

II. Claims 87-89, drawn to the genus of method of manufacturing an agent, classification dependent upon species.

III. Claims 90-91, drawn to the genus of an agent identified by a method detection, classification dependent on species.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related to as a method of detection and a method of manufacturing which includes steps of detection. While inventions I and II overlap somewhat in method steps, the outcomes are different, and patentability of invention II requires complete search of the preparation step, which is not required for invention I.

Inventions I and III are related as method of identifying and agent identified. The inventions are distinct because a search for the method will not reveal art as to the agent, or a search for the agent will not reveal art as to the method. Further, the agent can be identified by other means, via different activities or properties.

Invention III and invention II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP 806.05(h)). In the instant case the method of invention II can be practiced with a hedgehog protein, which is a materially different product.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for purposes as indicated is proper.

Applicant was required to elect a single genus for prosecution on the merits.

During a telephone conversation with Melissa Rones on 3 March 2004 a provisional election was made with traverse to prosecute the invention of group I, which includes claims 1-78 and 81-84. Affirmation of this election must be made by the applicant in responding to this office action. Claims 87-91 are withdrawn from further consideration by the Examiner, 37 C.F.R. 1.142 (b), as being drawn to a non-elected invention.

Claims 1, 3, 6-7, 17, 20-23, 26-27, 29-30, 32-36, 42-49, 63-76, 78 and 81-84 are under consideration.

Objections

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "Screening assays for hedgehog agonists and antagonists" is not descriptive because there are no claims directed to assays that include the hedgehog polypeptide and hence screen for antagonists of such.

Claim Objections

Claims 34 and 47-49 are objected to as being dependent upon a canceled base claim. These claims would be in proper form if rewritten to remove reference to the canceled claims. Claim 34 would be in proper form if Applicant removes the reference to canceled base claim 15. Claims 47-49 would be in proper form if Applicant removes the reference to canceled base claim 8. Claims 15 and 8 were each canceled by applicant in Paper No. 07/26/2001. Claims 34 and 47-49 will be examined as if the claims did not make reference to the respective canceled base claims.

Claims 68 and 69 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Multi-dependent claims 68-69 would be in the proper form if Applicant removes references to the multi-dependent claim 67.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78 and 81-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78 and 81-84 are drawn to an assay with a test compound, a patched protein (hedgehog receptor), and detecting activation of the hedgehog pathway. Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78 and 81-84 encompass cells lacking a native hedgehog pathway, for example, a yeast cell. Claim 1 additionally encompasses a cell-free reaction mixture. In the absence of other evidence in the specification, it is not clear that the hedgehog pathway would be activated in a cell lacking a native hedgehog pathway (such as a yeast cell), or in a cell-free reaction mixture. No description of such assays is provided in the specification. Page 63 lines 20-23 of the specification teaches "the gene products of one or more of *smoothened*, *costal-2*, and/or *fused* can be co-expressed with patched in the reagent cell, with assays being sensitive to the functional reconstitution of the hedgehog signal transduction cascade." The specification does not teach whether expression of only one, two, or all three of these genes is necessary and/or sufficient to reconstitute the hedgehog pathway in a cell lacking a hedgehog pathway. Expression of other genes may be necessary. For example, the gene *cubitus interruptus* is required in Drosophila for *patched* gene expression (Forbes, et al 1993). What is missing from the specification is a disclosure of whether the hedgehog pathway can be activated in a cell lacking a native hedgehog pathway, or a cell-free reaction mixture, how to do so. Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of filing

date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow person of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116). Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C § 112 is severable from its enablement provision (see page 1115).

The inventions of claims 23 and 84 are drawn to an assay "wherein the reporter gene includes a transcriptional regulatory sequence selected from a *GLI* gene and a patched gene." Claim 74 is drawn to an assay "wherein the transcriptional regulatory element is derived from target genes selected from the group consisting of *GLI*, *patched*, *cubitus interruptus*, and *fused*." The specification discloses, on page 64 that "by selecting transcriptional regulatory sequences from such target genes, e.g. from *patched* or *GLI* genes, that are responsible for the up- or down regulation of these genes in response to hedgehog induction, and operatively linking such promoters to a reporter gene, the present invention provides a transcription based assay which is sensitive to the ability of a specific test compound to influence hedgehog signaling pathways." Furthermore, the specification discloses "To identify potential regulatory elements responsive to hedgehog signaling present in the transcriptional regulatory sequence of a target gene, nested deletions of genomic clones of the target gene can be constructed using standard techniques." What is missing from the specification is a disclosure of the transcriptional regulatory sequences

of the *GLI*, *patched*, *cubitus interruptus*, and *fused* genes that are to be used in the reporter genes.

The inventions of claim 45 and 46 are drawn to assays wherein the cell is an oocyte, or a yeast cell, respectively. As described in the specification, page 62, line 36 to page 63, line 63 these cells "either express low levels or lack expression of the patched protein." In the absence of other evidence in the specification, it is assumed that these cells lack other components of the hedgehog signaling pathway. What is missing from the specification is a disclosure of such cells, comprising the elements needed for hedgehog signaling.

Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78 and 81-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention 2) state of prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working templates, 6) breadth of claims, 7) amount of direction of guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1, 3, 6, 7, 17, 20-23, 27, 29, 30, 32-36, 42-49, 63-76, 78 and 81-84 are rejected because while they are enabling for an assay in a cell with a functional hedgehog pathway, they are not enabled for cells lacking a native hedgehog pathway (for example, a yeast cell), or in the case of Claim 1, a cell-free reaction mixture. In the absence of other evidence in the specification, it is not predictable that the hedgehog pathway would be activated in a cell lacking a native hedgehog pathway (such as a yeast cell), or in a cell-free reaction mixture. No working examples are provided in the specification of assays in which cells lacking the hedgehog pathway or cell free systems were used. Page 63 lines 20-23 of the specification teach "the gene products of one or more of *smoothened*, *costal-2*, and/or *fused* can be co-expressed with patched in the reagent cell, with assays being sensitive to the functional reconstitution of the hedgehog signal transduction cascade." The specification does not disclose whether only one or all of these three are necessary and/or sufficient to reconstitute the hedgehog pathway in a cell lacking a hedgehog pathway. Other components may be necessary. For example, the gene *cubitus interruptus* is known to be necessary in Drosophila for *patched* gene expression (Forbes, et al 1993). What is missing from the specification is a disclosure of whether the hedgehog pathway can be activated in a cell lacking a native hedgehog pathway or a cell-free reaction mixture. To use the instantly claimed assays would require undue experimentation to determine if the hedgehog pathway is functional in cells lacking a native hedgehog pathway or in a cell-free reaction mixture, and if not, to determine what additional components are necessary for reconstitution of the pathway.

Claim 45 is rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a *Xenopus* oocyte, does not reasonably provide enablement for other oocytes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification teaches assays involving *Xenopus* oocytes; see for example Example 12. The use of *Xenopus* oocytes is old and well known in the art. It is routine in the art to use *Xenopus* oocytes, and not routine to use other non-*Xenopus* oocytes. The prior art does not teach culture methods for non-*Xenopus* oocytes that would allow the assays claimed to be practiced. It is well known the art that *Xenopus* oocytes have many properties that mammalian oocytes lack, that make them a useful experimental system. There are no examples or guidance in the specification for the instant invention for use of non-*Xenopus* oocytes, which includes mammalian oocytes. To use the instantly claimed assays would require undue experimentation to develop a model system using non-*Xenopus* oocytes.

Claims 17, 63 and 78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for naturally occurring patched receptors, does not reasonably provide enablement for proteins having sequences other than these. Claim 63 is directed to assays using "cells expressing a *patched* protein" and claims 17, 78 are directed to assays using "...a cell expressing a hedgehog receptor, wherein said hedgehog receptor binds a naturally occurring hedgehog polypeptide..." These proteins include undisclosed non-naturally occurring patched receptors or undisclosed naturally or non-naturally occurring hedgehog receptors that may be distinct from patched. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The inventions of claims 23 and 84 are drawn to an assay "wherein the reporter gene includes a transcriptional regulatory sequence selected from a *GLI* gene and a patched gene." Claim 74 is drawn to an assay "wherein the transcriptional regulatory element is derived from target genes selected from the group consisting of *GLI*, *patched*, *cubitus interruptus*, and *fused*." The specification does not disclose the transcriptional regulatory sequences of the *GLI*, *patched, cubitus interruptus*, and *fused* genes that are to be used in the reporter genes. Without any guidance provided by the inventor to these sequences, one of ordinary skill in the art would require an undue quantity of experimentation needed to determine these sequences in order to make or use the invention.

The inventions of claim 45 and 46 are drawn to assays wherein the cell is an oocyte, or a yeast cell, respectively. As described in the specification, page 62, line 36 to page 63, line 63 these cells "either express low levels or lack expression of the patched protein." In the absence of other evidence in the specification, it is assumed that these cells lack other components of the hedgehog signaling pathway. Without any guidance provided by the inventor as to what components are necessary to reconstitute the hedgehog pathway in these cells, one of ordinary skill in the art would require an undue quantity of experimentation to test these components in order to make and use the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6-7, 17, 20-23, 26-27, 29-30, 32-36, 42-49, 63-76, 78 and 81-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 17, 30 and 78 are indefinite because it is unclear what qualifies as "statistically significant". The means of determining significance is not disclosed or recited.

Claim 7 uses indefinite language (i.e. "...wherein the recombinant cell *substantially* lacks expression..."). Because this phrase does not have a specific or unambiguous definition, it is unclear what Applicants intend or what this phrase includes or excludes, rendering claims using this language vague and ambiguous.

Claims 17, 63 and 78 use indefinite language (i.e. "...a hedgehog receptor..." or "...a patched protein..."). Because these phrases do not have a specific or unambiguous definition, it is unclear what Applicants intend or what this phrase includes or excludes, rendering claims using this language vague or ambiguous. The terms hedgehog receptor and patched protein are not defined in the specification as being limited to a naturally occurring patched receptor recognized as having the structure disclosed in Figure 22. Because the phrase "patched protein" and "hedgehog receptor" in the claims is different from "naturally occurring patched receptor", it is assumed

Applicant intends a different meaning. For example, these terms encompass undisclosed non-naturally occurring patched receptors or undisclosed naturally or non-naturally occurring hedgehog receptors that may be distinct from patched.

Claims 21-23, 48, 65 and 82-84 are indefinite due to improper Markush language. These claims would be definite if Applicant amended the portion of the claims reading "...selected from..." to read "...selected from the group consisting of..."

Claim 23 recites the limitation " the assay of claim 20, wherein the reporter gene includes a transcriptional regulatory sequence of a gene selected from a *GLI* gene and *patched* gene ". Claim 23 is indefinite because it is unclear if the transcriptional regulatory sequence is to be selected from either *GLI* or patched, or from a combination of both. Claim 23 would be definite if Applicant amended the claim to recite, "the assay of claim 20, wherein the reporter gene includes a transcriptional regulatory sequence of a gene selected from the group consisting of a *GLI* gene and *patched* gene".

The metes and bounds of claim 29 are unclear because it is not known what is meant by "homologs" of. Neither the specification nor the art provide a single meaning for the term so that the skilled artisan would understand the breadth of the term. The specification describes "homology" as referring to sequence similarity (p. 26, last paragraph). It is unclear in the instant claim how much sequence identity and degree of relatedness is necessary for two proteins to be "homologs". See Reeck et al. (EQ, submitted by the Applicants) for a discussion of the confusion in biology about the meaning of the term.

Claim 29 is also indefinite because it is unclear whether the heterologous gene constructs in the cell are expressed or are just present.

Claim 30 is indefinite because it the assay "to identify agents that activate hedgehog signal transduction" does not include the hedgehog protein. It is not clear how hedgehog signal transduction can be activated when the hedgehog protein is not present. The applicants may be referring to the "hedgehog pathway" as recited in claims 1 and 17. However, because the phrase "hedgehog signal transduction" is different from the phrase "hedgehog pathway", it is assumed Applicant intends a different meaning.

Claim 47 uses the term "variegated" which is a relative term that renders the claim indefinite. The term "variegated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree (the term variegated is used on line 35 of page 12 of the specification but is not further defined), and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The use of term variegated renders indefinite the library of claim 47.

Claim 47 is also indefinite because it is unclear whether the steps of the assay are to be repeated once with the entire library of 100 compounds, or whether the steps of the assay are to be repeated 100 times with each compound individually.

Claim 49 is indefinite because it presents an additional method step without relating it to the method of the claims from which it depends. It is unclear at what point in the method the pharmaceutical composition is to be prepared. It is also unclear how to "prepare" the pharmaceutical composition.

Claim 63 is indefinite because it is unclear how comparing the responses leads to the identification required by the preamble. Clarity could be added to the claim by adding at the end a phrase such as, "wherein the presence of a hedgehog agonist is indicated by a _____ (e.g., identical, two fold increased) response in said cells to the test agent compared to similar cells in response to a naturally occurring hedgehog protein..." Note that there must be basis in the specification for the type of response and the suggestions made by the examiner do *not* necessarily have basis but are intended to present the general idea of concepts that may be suitable.

Claim 65 recites the limitation "said detectable response comprises expression of secondary signaling molecules selected from Bmp-2, Bmp-4, and Fgf-4". Claim 65 is dependent on claim 64 which recites, "...the said detectable response comprises expression of a gene controlled..." Claim 65 is dependent of claim 64 but fails to further limit the expression of a gene. Claim 65 would further limit claim 64 if Applicant amended claim 65 to read, "...said detectable response comprises expression of a gene selected from the group consisting of genes encoding Bmp-2, Bmp4, and Fgf-4."

Claim 70 is rejected under 35 USC 112, 2nd paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP 2172.01. The omitted elements are: the connection between 1) the detecting level of the expression of said reporter gene, and 2) the comparing the response of said cells to a test agent. It is unclear if the comparing is meant to be comparing of the response of levels of reporter gene expression in the presence compared to the

absence of the test agent, or if the two elements are connected in some other undisclosed manner.

Claim 71 is indefinite because it is unclear whether the expression of the reporter gene is detected by determining what reporter gene protein product is produced, or whether the expression is detected by determining how much reporter gene protein product is produced.

Claim 72 is indefinite because it is unclear what is meant by "detected by an intrinsic activity".

Claim 73 is indefinite because it is unclear what is meant by "...detected by an enzymatic activity..." Claim 73 would be definite if amended to read, "...detected by assaying for an enzymatic activity..."

Claim 74 recites the limitation "a method of claim 63 or 70, wherein the transcriptional regulatory element." There is insufficient antecedent basis in Claim 63 for this limitation. Claim 63 makes no reference to a transcriptional regulatory element.

Claim 74 is also indefinite because it is unclear how the transcriptional regulatory element is derived from target genes. The term "derived" is not defined in the specification.

Claim 74 is also indefinite because it is unclear how "the transcriptional regulatory element" is derived from multiple target genes. In this regard, the claim would be definite if amended to recite "...a target gene selected from the group consisting of..."

Claim 75 is indefinite because it is dependent on claim 70 and it is unclear how the homeobox genes recited in claim 75 are related to the reporter gene construct in claim 70.

Claim 76 recites the limitation "homeobox gene". There is insufficient antecedent basis for this limitation in the claim. Claim 75, upon which this depends, requires "homeobox genes" – plural. There is no basis for a single gene.

Claim 76 recites the limitation "wherein the homeobox gene is Hoxd." Several Hoxd genes are referred to in the specification. Page 138, lines 31-32 discloses "The best candidates for genes regulated by Sonic in vivo are the distal members of the Hoxd gene cluster, Hoxd-9 through -13, and Bmp-2". It is unclear whether this claim is reciting all or only one of the disclosed Hoxd genes.

Claim 78 in indefinite because it is drawn to "an assay for screening test compounds to identify agents that antagonize a bioactivity of a hedgehog protein..." but it is unclear whether any of the following method steps include the hedgehog protein.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 6-7, 17, 20-23, 26-27, 30, 33-36, 42-44, 46, 63-64, 66-70, 74, 78, and 81-84 are rejected under 35 U.S.C. 102(e) as being anticipated by Scott, US Patent 5,837,538. These claims encompass use of an assay in which a naturally occurring patched receptor is present and a hedgehog protein is not present and merit priority to the first disclosure of an assay of this nature in the claims section of the parent application 08/356060 of 07/02/1996. Scott teaches use of an assay with a naturally occurring patched receptor in the specification of US Patent 5,837,538, which merits priority to the disclosure in the specification of application 08/319,745 filed 10/7/1994.

Scott teaches, in column 1, line 30, a "transmembrane protein called patched (PTC)", and in column 7, line 56 that "The PTC protein...may be employed in a wide variety of assays" and in column 8, lines 5 through 11 that "The assays may be used...for identifying molecules which may serve as agonists or antagonists" and in column 8, lines 12-40 that a format "may be designed where the cells respond when an agonist binds to PTC in the membrane of the cell. An expression cassette may be introduced into the cell, where the transcriptional initiation region of patched is joined to a marker gene...When an agonist binds to the PTC protein, the cell will turn blue." The specification of the instant invention does not define the test compound or place any limits on its definitions. Both Scott (in column 2 lines 30-40) and the specification of the instant invention (page 12 lines 13-14) teach response of the *patched* gene as part of the hedgehog pathway. Accordingly, Scott anticipated an invention with all of the limitations of claim 1. Claim 63 is rejected for the same reasons.

Claim 3 of the instant invention is directed to "the assay of claim 1, wherein the reaction mixture comprises a cell including a heterologous nucleic acid recombinantly expressing the patched receptor". Scott teaches, in column 5, lines 1-10 that "The DNA sequence encoding PTC may be may be isolated as the sequence substantially free of wild-type sequence from the chromosome, ...may be joined to heterologous or foreign DNA..." and in column 5, lines 1-10 that the "subject gene may be introduced into an appropriate vector for extrachromosomal maintenance or for integration into the host." Scott further teaches "For large production of the protein, a unicellular organism or cells of a higher organism may be used". Finally, Scott teaches in column 17 lines 64 through column 18 lines 58 "mammalian patched genes are provided which allow for high level production of the patched protein, which can serve many purposes...The patched protein may be used in a screening for agonists and antagonists." Accordingly, Scott anticipates an invention with all of the limitations of claims 3 of the instant invention.

Claim 6 of the instant invention recites "The assay of claim 3, wherein detecting activation of the hedgehog pathway comprises detecting change in the level of expression of a gene controlled by a transcriptional regulatory sequence responsive to signaling by the patched polypeptide." As described above for claim 1, Scott teaches an assay wherein detecting change in the level of expression of hedgehog pathway comprises detecting change in the expression of the patched gene transcriptional regulatory sequence. Accordingly, Scott anticipates an invention with all of the limitations of claim 6 of the instant invention.

Claim 7 of the instant invention recites "The assay of claim 3, wherein the recombinant cell substantially lacks expression of an endogenous patched receptor". Scott teaches, in column 5, lines 33-35 producing a recombinant cell expressing the patched receptor, wherein the host cell is "*E. coli*, *B. subtilis*, *S. cerevisiae* and the like" These organisms lack expression of an endogenous patched receptor. Accordingly, Scott anticipates an invention with all of the limitations of claim 7 of the instant invention.

Claims 17 and 78 of the instant invention recites an assay comprising a cell expressing a hedgehog receptor, contacting the cell with a test compound, and detecting activation of the hedgehog pathway. The patched protein is a hedgehog receptor. As described above for claim 1, Scott anticipates an invention with all of the limitations of claims 17 and 78 of the instant invention.

Claims 20 and 81 are rejected for the same reasons as claim 6.

Claim 21 recites "the assay of claims 20 or 33, wherein the reporter gene encodes a gene product that gives rise to a detectable signal selected from color, fluorescence, luminescence, cell viability, relief of a cell nutritional requirement, cell growth, and drug resistance." As described above for claim 1, Scott recites an assay wherein the reporter gene encodes a gene product that turns the cell blue. Accordingly, Scott anticipates an invention with the limitation of a color detectable signal as described in claim 21. Claim 82 is rejected for the same reason.

Claim 22 recites "the assay of claim 21, wherein the reporter gene encodes a gene product selected from chloramphenicol acetyl transferase, luciferase, betagalactosidase, and alkaline phosphatase." Scott teaches, in column 8 lines 17-18

an assay "where the transcriptional initiation region of patched is joined to a marker gene, such as B-glycosidase." Accordingly, Scott anticipates an invention with the limitation of claim 22 of a reporter gene which encodes a betagalactosidase gene product. Claim 83 is rejected for the same reason.

Claim 23 recites "the assay of claim 20, wherein the reporter gene includes a transcriptional regulatory sequence of a gene selected from a *GLI* gene and *patched* gene." As described above for claim 1, Scott anticipates an invention of an assay using the transcriptional regulatory sequence from a patched gene. Claim 84 is rejected for the same reason.

Claim 26 rejected for the same reasons as claim 1.

Claim 27 is rejected for the same reasons as claim 3.

Claim 30 is rejected for the same reasons as claim 1 and 3.

Claim 33 is rejected for the same reasons as claim 6.

Claims 34-36 recite assays wherein the patched protein is respectively vertebrate, mammalian, or human patched protein. Scott teaches assays using any patched genes and in column 6 lines 27-29 discloses the sequence of the human patched gene. Accordingly, Scott anticipates assays in which the patched protein is vertebrate, mammalian or human.

Claim 42 recites "an assay of any of claims 3, 17, 30, or 78, wherein the cell is a metazoan cell". In claim 43 recites "an assay of claim 42 wherein the cell in a mammalian cell". Scott teaches, in column 8 line 13, using mammalian cells in the assays. Mammalian cells are metazoan cells. Scott anticipates all of the limitations of

claims 42 and 43 of the instant invention. Claims 67, 68 and 69 are rejected for the same reason. Furthermore, Scott teaches, in column 5, lines 36-39, "in many situations, it may be desirable to express the patched gene in a mammalian host..." It is well known in the art that the process of introduction of DNA into a eukaryotic cell (for example, mammalian) and integration into the chromosome is known as transfection. Therefore, Scott inherently anticipates all of the limitations of claim 66, which recites "a method of claim 63, wherein said cells are transfected to express a recombinant form of the patched protein."

Claim 44 recites "the assay of claim 42, wherein the cell is an insect cell". Scott teaches in column 8, lines 13-15 that "invertebrate cells may be designed where the cells respond when an agonist binds to PTC in the membrane of the cell" and teaches in column 12, lines 3- "a series of constructs were designed that link different regions of the ptc promoter from *Drosophila* to a LacZ reporter gene...these expression cassettes were introduced into *Drosophila* lines". *Drosophila* is an insect. Accordingly, Scott anticipates an invention with the limitation of claim 44 wherein the assays are conducted using an insect cell.

Claim 46 recites "the assay of any of claims 3, 17, 30, or 78, wherein the cell is a yeast cell." Scott teaches in column 5, line 34 use of a yeast cell for expression of the patched protein. " Scott teaches in column 17 lines 64 through column 18 lines 58 "mammalian patched genes are provided which allow for high level production of the patched protein, which can serve many purposes...The patched protein may be used in

a screening for agonists and antagonists." Accordingly, Scott anticipates an invention with all of the limitations of claim 46 of the instant invention.

Claims 64 and 70 are rejected for the same reasons as claim 6.

Claim 74 is rejected for the same reason as claim 23.

Claims 32 and 47-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Scott #2, US Patent 6027882 5/31/1996. Claim 47 recites an assay wherein "the steps of the assay are repeated for a variegated library of at least 100 different test compounds". Claim 48 recites an assay wherein "the test compound is selected from small organic molecules and natural product extracts". Claim 49 recites an assay "further comprising preparing a pharmaceutical preparation of one or more compounds identified." The limitations of claims 47, 48 and 49 are drawn to material first disclosed in pages 12, line 35 to page 13, line 2 of the specification of application 08/674509 7/2/1996 and thus are enabled for a priority date of 7/2/1996.

Claim 32 recites, "The assay of claim 30, wherein the cell is a human cell". Scott #2 teaches, in column 13, lines 40-45 that "Other assays of interest detect agents that mimic patched function...For example, an expression construct comprising a patched gene may be introduced into a cell line under conditions that allow expression." Scott #2 further teaches in column 12 line 33-34 "Of particular interest are screening assays for agents that have a low toxicity for human cells." Accordingly, Scott #2 inherently anticipates all of the limitation of claim 32, including a screening assay using human cells recombinantly expressing patched protein.

Scott #2 teaches, in column 12 an assay involving patched gene product, a test compound, and detecting transcriptional changes mediated. Scott #2 further teaches in column 12, lines 66 to column 13, line 1 that "candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds." Claim 47 of the instant invention recites "wherein the steps of the assay are repeated for a variegated library of 100 different test compounds." The specification of the instant invention does not point out any particular reason why at least 100 different test compounds are to be used and in the absence of any other evidence, one of ordinary skill in the art would be as likely to use 50 or 150 different test compounds. Accordingly, the "wide variety of sources" of test compounds taught by Scott #2 anticipates all of the limitations of claim 47 of the instant invention. Scott #2 teaches in column 12, lines 51-53, "candidate agents encompass numerous chemical classes, ...preferably small organic compounds..." Accordingly, Scott #2 anticipates all of the limitations of claim 48 of the instant invention. Scott #2 teaches "the compounds having the desired pharmacological activity may be administered in a physiologically acceptable carrier to a host". Accordingly, Scott #2 inherently anticipates the limitation of claim 49 of teaching the preparation of a pharmaceutical preparation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 65 is rejected under 35 U.S.C. 103(a) as being unpatentable over Scott, US Patent 5,837,538 as applied to claim 63 above, and further in view of Niswander, et al 1994. Claim 65 recites "a method of claim 64, wherein said detectable response comprises expression of secondary signaling molecules selected from Bmp-2, Bmp-4, and Fgf-4". Claim 64 is in dependent on claim 63. As described above, Scott teaches all of the limitations of claims 63 and 64. Scott does not teach the limitations of claim 65 that "wherein said detectable response comprises expression of secondary signaling molecules selected from Bmp-2, Bmp-4, and Fgf-4". Niswander teaches, on page 610, that Shh expression induces Fgf-4 expression. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute Fgf-4 expression for patched gene expression (the example taught by Scott). The person of ordinary skill in the art would have been motivated to make that modification because, in

the absence of any evidence to the contrary, they would have expected identical results in an assay for test agents which stimulate the hedgehog pathway where Fgf-4 expression was substituted for patched gene expression, and reasonably would have expected success because Niswander teaches how to detect Fgf-4 expression in cells in response to a hedgehog protein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard, Ph.D. whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D. can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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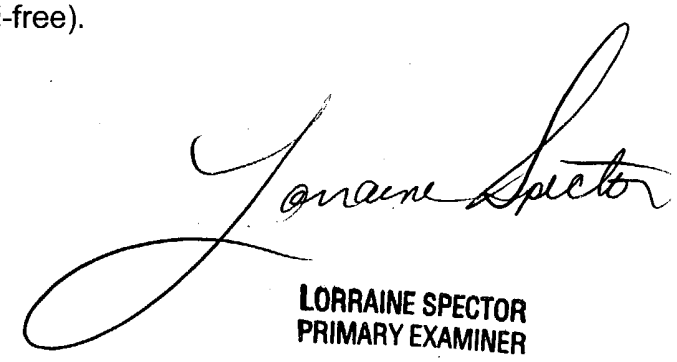

LORRAINE SPECTOR
PRIMARY EXAMINER